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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/728,357	DOUCETTE ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *9-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/4/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/30/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Application, filed December 4, 2003, claims no priority.

Claims 1-20 are pending.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-8, in the reply filed on January 21, 2005 is acknowledged.

Claims 9-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on January 21, 2004.

Group I, claims 1-8, drawn to a method of inducing a permanent change in the neurological development of a rodent, wherein said rodent is administered a kainate receptor agonist and wherein rodent exhibits reproducible seizure-like symptoms following kainate receptor agonist administration, is under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing a permanent change in the neurological development of a rat, comprising treating a rat during the second post natal

week with doses of domoate as low as 5 ug/kg and as high as 20ug /kg for male rats, 20 ug/kg of domoate for female rats, and doses as low as 25 ug/kg and as high as 100 ug/kg of kainate for male and female rats, wherein the rat exhibits seizure-like symptoms upon exposure to a mild or moderate stressor that would normally not elicit a seizure, does not reasonably provide enablement for a method of treating any rodent during the second post natal week with any doses of any kainate receptor agonist, wherein the rodent exhibits seizure-like symptoms upon exposure to mild or moderate stressor that would normally not elicit a seizure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant invention is to a method of generating a rat model of epilepsy, wherein treatment with a kainate receptor agonist during the second postnatal week results in rats with a permanent change in neurological development and seizure-like symptoms.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many

factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims broadly encompass any treatment with kainate receptor agonist during the second postnatal week can be used to induce a permanent neurological change in a rodent wherein said rodent exhibits reproducible seizure-like symptoms. The art at the time of filing teaches that the hippocampus of immature rats does not undergo seizure-induced synaptic reorganization. Sperber et al. (1991, Developmental Brain Research 60: 88-93, see IDS) teach that 15 day-old rat pups and adult rats were exposed to kainic acid (5mg/kg and 15mg/kg) (Sperber et al., page 88, 2nd col., 3rd parg.). 2-4 weeks following kainic acid seizures, rat brains were assesed for seizure-induced changes. Cresyl violet and Timm staining of adult rats demonstrated significant cell loss in the CA3 of the hippocampus and the presence of mossy fiber reorganization in the supragranular layer of the dentate. In the case of the rat pups, seizure-induced cell loss of synaptic sprouting was not apparent in sections (Sperber et al., page 89, 2nd col., 2nd parag.). In addition to this, paired-pulse perforant path stimulation profiles indicated enhancement of paired-pulse inhibition in adult rats, whereas rat pups did not demonstrate any difference (Sperber et al., page 89, 2nd col., 3rd parag. and Fig. 2). In

the method described by Sperber, et al., rat pups did not demonstrate any neurological changes, while adult rats did, following kainic acid-induced seizures. While the claim is to a broad scope for any treatment method, the art teaches that there are methods that do not produce rats that exhibit permanent neurological change and reproducible seizure-like symptoms. In order to generate a rat that exhibits seizure-like symptoms when exposed to a mild or moderate stressor, wherein the rat had been treated with low doses of kainate receptor agonist during the second postnatal week, an artisan would need to be taught parameters of how to make these rats, including dosage, which kainate agonist to use, frequency and duration of dosing, and age at which animals receive treatment. These must be empirically determined. For this reason, the specification does not enable any method of generating a rat comprising permanent neurological change and reproducible seizure-like symptoms, wherein the parameters such as which kainate agonist, the dosage, frequency and duration of dosing, and age at which animals receive treatment are not taught.

With regards to any treatment during the second post natal week that can be used to induce a permanent neurological change in a rodent, the specification teaches that male and female rats were injected with either 20 ug/kg, 5 ug/kg, or 0ug/kg of domoic acid (DOM). In Figure 1b of the specification, female rats treated with 5ug/kg of DOM did not exhibit any NIS-L. According to these results, a skilled artisan would not know how to use any female rat treated with 5 ug/kg of DOM. Nothing in the specification teaches how to use a rat treated with 5ug/kg of DOM that does not exhibit any symptoms of a seizure. For this reason, the specification does not enable an

artisan to use female rats treated postnatally from day 8 to day 14 with 5ug/kg of DOM. The specification also does not teach how to use doses greater than 20 ug/kg of DOM such that the rats exhibit seizures, and are comprised of permanent changes in neurological development. The specification does not teach how to use doses less than 20 ug/kg of DOM on female rats, such that the rats exhibit seizures and are comprised of permanent changes in neurological development. Similarly, the specification does not teach how to use doses of kainic acid less than 25 ug/kg (note, see Example 3, specification, page 15, lower level of KA used was 25 ug/kg), such that rats were comprised of permanent changes in neurological development and exhibited seizures. With regards to using 5 to 50 g/kg of DOM or 10 to 100 g/kg of kainic acid (see claims 5-8), the specification teaches that ug/kg dosages were used. Nothing in the specification or the art teaches how to generate rat models of epilepsy using these dosages. With regards to identifying upper limits of drug dosage that could be used, there is undue experimentation involved because the specification does not provide guidance as to the highest or lowest amount of domoate or kainate one could use such that the rats exhibit the same phenotypes described in the specification.

With regards to any route of administration of a kainate receptor agonist, the specification teaches that domoic acid and kainic acid were administered to rats subcutaneously. Futher, the art teaches that kainic acid and domoic acid can be administered intraperioteally (e.g. Doucette,et al., 2000, Neurotoxicology and Teratology, 22: 863-869, see IDS page 865, 1st col., 1st parag.). The art teaches that domoic acid and kainic acid are water soluble (e.g. they are dissolved in sterile

physiological saline, Doucette et al., page 864, 2nd col., 2nd parag.). While the art teaches these embodiments, the art does not teach other methods of administration, such as how to administer domoic acid or kainic acid orally, or as an ointment, or what concentration of domoic acid or kainic acid should be used to should these compounds be administered orally or in an ointment. To demonstrate that kainic acid or domoic acid can be administered orally or in an ointment would be undue experimentation as an artisan would need to learn how quickly is the drug absorbed, how quickly does the drug take to get to the site of interest, and how quickly does the drug leave the site of interest. For these reasons, the specification only enables an artisan to administer domoic acid or kainic acid either via intraperitoneally, or intravenously.

With regards to any rodent, the art teaches that the subunits of the kainate receptor are not conserved amongst rodent species. For example, the art teaches that there is no alternative splicing of KA1, KA2, or GluR6 in the rat, although there is alternative splicing in other species (Ruscheweyh, et al., 2000, Brain Research Reviews, 40: 215-222; page 216, 1st col., 2nd parag. under "Functional Properties"). The specification at the time of filing teaches how to administer domoate and kainate to rats; however, the specification does not teach how to predictably administer domoate and kainate to other rodent species such as mice, rabbits, and guinea pigs, such that these rodents can be used as seizure models. For this reason, while the specification is enabling for rats, it does not provide enablement for the broad scope of all rodents.

Claim 1 is broadly written such that any kainate receptor agonist can be used to generate a rodent with seizure-like symptoms. The art at the time of filing teaches that

in addition to kainaic acid and domoic acid, other agonists of the kainate receptor complex exist. One example is APTA ((RS)-2-amino-3-(3-hydroxy-5-tert-butylisoxazol-4-yl) propanoic acid). The art teaches that ATPA targets the GluR5 subunit of the kainate receptor (Clarke, et al., 1997, Nature, 389: 599-603). The art teaches that while the domoate and kainate are water soluble, and thus, one would not expect a difference of bioavailability when domoic acid is injected intraperitoneally or subcutaneously (Doucette, et al., 2000, Neurotoxicology and Teratology, 22: 863-869, page 868, 1st col., 1st parag., lines 16-20), the art teaches that ATPA is bulky and lipophilic, which contributes to what determines receptor selectivity between AMPA and GluR5 receptors (Johansen et al., 2003, Chirality, 15: 167-179, page 176, 1st col., 1st parag.). Due to these differences in solubility, a skilled artisan would not administer APTA in the same way one would administer kainate or domoate. Rather, the route of administration would be different and the specification, at the time of filing, does not teach how to administer a lipophilic drug to target GluR5 containing kinate receptors in the brain, such that APTA could be used to generate a rodent that exhibits seizure-like symptoms. In addition to this, work by Khalilov et al. (2002, J. Neurophysiolo., 88:523-527) teaches that ATPA prevents the propagation of seizures from one hemisphere to the other. Khalilov et al. teach that in patch-clamp recordings of both hemispheres, application of high potassium concentrations (7mM), bicuculine (3uM) or 4-AP (50uM) generated episodes (Khalilov et al., page 524, 2nd col., 2nd parag.). However, addition 1uM of APTA did not (Khalilov et al., page 525, 1st col., 1st parag.). While Khalilov et al. are not completely certain what the underlying differences are between kainate and

ATPA such that a seizure is generated or not, Khalilov et al. teach that GluR5-containing receptors can prevent the propagation of seizures from one hemisphere to the other. Further, Khalilov et al. teach, based on their result, that the end result (i.e. seizure), is mediated by different subunits of the kainate receptor (Khalilov, et a., page 526, 1st col., 4th parag.). For these reasons, the art does not enable a skilled artisan to practice the invention using any kainate receptor agonist.

With regards to any kainate receptor agonist, the art teaches that there are multiple forms of domoic acid. A search of the Sigma Chemical's online catalog shows that there are two forms of domoic acid (Sigma catalog number D6152 is one form and Fluka catalog number 44246 is the other). Nothing in the Sigma catalog or in the specification provides guidance as to which compound should be used in the instant invention, nor does the Sigma catalog of the specification teach what dosage should be used for the different domoates. Alternatively, nothing in the Sigma catalog or the specification teaches that both compounds can be used exactly the same way.

For the reasons described above, the specification and art do not enable a skilled artisan to practice the claimed invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant invention is to a method of generating a rat model of epilepsy, wherein treatment with a kainate receptor agonist during the second postnatal week results in rats with a permanent change in neurological development and seizure-like symptoms.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at http://www.uspto.gov/web/menu/current.html#register).

The written description requirement for a claimed genus is satisfied by sufficient description of a representative number of species by actual reduction to practice and by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant were in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The claims are broad for any kainic acid agonist. However, the specification does not teach an artisan how to generate any chemical compound and know that it

interacts with a kainate receptor and has an agonist effect. The specification does not teach, for example, the structure of the active site of a kainate receptor, such that if a chemical compound were to interact with it, a conformation change would occur and activate the receptor. Similarly, the specification does not teach the structure of chemical compounds which would predictably interact with the kainate receptor and have an agonistic effect.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the specification does not teach predictable ways to generate and identify other kainic acid receptor agonists. In addition to this, the specification does not teach the structure of a kainate receptor such that one might design chemical compounds that interact with it. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d

1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only kainic acid and domoic acid meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant's attention is drawn to the decision of *The Regents of the University of California v. Eli Lilly and Company* (CAFC, July 1997) wherein it was stated:
In claims involving chemical materials, generic formulas usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate written description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot,

as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See *Fiers,* 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen*). It is only a definition of a useful result rather than a definition of what it achieves as a result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. *See In re Wilder*, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

Because Applicants have failed to provide an adequate written description of the materials used in the compositions and methods claimed and because there is no evidence that Applicants possessed any kainate receptor agonists embodiments beyond those disclosed and/or known in the prior art, the rejected claims fail to meet the written description requirement under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 uses the word, "reproducible" to describe the seizure-like symptoms. This is a relative terms and it is unclear whether "reproducible" refers to the fact that the seizure is reproducible between a group of rats or if the seizure is reproducible in one rat, exhibiting a seizure-like symptom, each time provoked with a mild stressor.

Claim 1 uses the word, "low" to describe the level of dose of a kainate receptor agonist. "Low" is a relative term, depending upon the context of use. One artisan's "low" is another artisan's "high." Similarly, claim 1 uses "mild" and "moderate" to describe stressor. Again, these are relative terms and the use of these words depend upon the application used by the artisan.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH

With regards to a method of inducing a "permanent change." Rats are sacrificed at 16 months. Does art teach that hippocampus ever recovers rapidly from kainate insult? Note that the art teaches that there is no hippocampal damage to young mice treated with kainate (Sperber, 1991). Was the BDNF/oxytocin enough data to demonstrate change in brain? BDNF, probably, in that the gene appears to be upregulated when there is cellular damage. Oxytocin, probably less so since art teaches that one epileptic event turns on oxytocin for prolonged period.

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER